**Amendments to the Specification:**

Please replace the paragraph beginning on page 3, lines 4-9 with the following amended paragraph:

It has now been discovered that ~~quinolones~~pyrrolidones having novel structures effectively inhibit the replication of HIV, including drug resistant strains of the virus. Selected ~~quinolones~~pyrrolidones of the invention are potent reverse transcriptase inhibitors. Accordingly, the present invention provides pharmaceutical compositions, and prophylactic and therapeutic treatments, diagnostic and prognostic methods and kits, and pharmaceutical screening methods that take advantage of the anti-HIV activity of the ~~quinolones~~pyrrolidones.

Please replace the paragraph beginning on page 3, lines 10-20 with the following amended paragraph:

Because the ~~quinolones~~pyrrolidones of the invention inhibit HIV replication, the prophylactic or therapeutic administration of the ~~quinolones~~pyrrolidones is a treatment for HIV infection. Prophylactic treatments are especially useful for persons at high risk of HIV infection. Thus, the present invention provides methods of inhibiting HIV replication in a person by administering to the person a pharmaceutically effective amount of a ~~quinolone~~pyrrolidone. This invention also provides pharmaceutical compositions comprising one or more ~~quinolones~~pyrrolidones in a pharmaceutically acceptable carrier. The compounds of the invention can be administered orally, parentally (including subcutaneous injection, intravenous, intramuscular, intrasternal or infusion techniques), by inhalation spray, topically, by absorption through a mucous membrane, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants or vehicles.

Please replace the paragraph beginning on page 3, line 23 to page 4, line 2 with the following amended paragraph:

In another aspect, the present invention provides a composition including at least one ~~quinolone~~pyrrolidone and a second therapeutic agent or agents. In an exemplary embodiment, the second therapeutic agent is used to prevent or treat HIV infection. In another embodiment, the second therapeutic agent is used to treat an opportunistic infection associated

with HIV infection. The second therapeutic is, for example, a protease inhibitor, a non-nucleoside reverse transcriptase inhibitor, a nucleoside reverse transcriptase inhibitor, an antiretroviral nucleoside, an entry inhibitor, or any other anti-viral agent effective to inhibit or treat HIV infection. In another embodiment, the second therapeutic agent is selected from the group consisting of zidovudine, didanosine, stavudine, interferon, lamivudine, adefovir, nevirapine, delaviridine, loviride, saquinavir, indinavir, and AZT. In another embodiment, the second therapeutic agent is an antibiotic or acyclovir. In still a further embodiment, the second agent is selected from immunomodulators, and entry inhibitors.

Please replace the paragraph beginning on page 4, lines 3-6 with the following amended paragraph:

In another aspect, the present invention provides methods of treating or preventing HIV infection in a human comprising administering a ~~quinolone~~pyrrolidone of the invention to a subject. As discussed above, the ~~quinolone~~pyrrolidone is optionally combined with one or more additional therapeutic agents.

Please replace the paragraph beginning on page 4, lines 7-11 with the following amended paragraph:

The invention also provides ~~quinolones~~pyrrolidones that are of use for inhibiting the replication of drug resistant, including multi-drug resistant, HIV mutants. The compounds of the invention have low cytotoxicity and display high potency against HIV and drug resistant strains of HIV. The compounds have been shown to inhibit replication of clinically observed drug resistant strains of HIV.

Please replace the paragraph beginning on page 4, lines 12-16 with the following amended paragraph:

In another aspect, the present invention provides methods of inhibiting HIV infection in a $CD4^+$ culture comprising the step of contacting the cell with a ~~quinolone~~pyrrolidone of the invention, either alone or in combination with a second therapeutic agent or a combination of other therapeutic agents. In one embodiment, the therapeutic agent or agents are used to treat or prevent HIV infection.

Please replace the paragraph beginning on page 4, lines 24-29 with the following amended paragraph:

The present invention provides new compositions and methods for preventing or ameliorating viral, *e.g.*, HIV infection, killing virally infected cells, *e.g.*, HIV infected cells and generally, inhibiting viral, preferably HIV, replication. The present invention is, in part, based on the surprising discovery that the ~~quinolones~~pyrrolidones of the invention effectively inhibit HIV infection, kill HIV infected cells and/or prevent HIV infection in the individual. Moreover, the compounds of the invention inhibit the replication of drug resistant strains of HIV.

Please replace the paragraph beginning on page 5, lines 16-23 with the following amended paragraph:

"Non-covalent protein binding groups" are moieties that interact with an intact or denatured polypeptide in an associative manner. The interaction may be either reversible or irreversible in a biological milieu. The incorporation of a "non-covalent protein binding group" into a ~~quinolone~~pyrrolidone of the invention provides the compound with the ability to interact with a polypeptide in a non-covalent manner. Exemplary non-covalent interactions include hydrophobic-hydrophobic and electrostatic interactions. Exemplary "non-covalent protein binding groups" include anionic groups, e.g., phosphate, thiophosphate, phosphonate, carboxylate, boronate, sulfate, sulfone, thiosulfate, and thiosulfonate.

Please replace the paragraph beginning on page 5, lines 27-33 with the following amended paragraph:

The term "targeting group" is intended to mean a moiety that is: (1) able to actively direct the entity to which it is attached (e.g., a ~~quinolone~~pyrrolidone) to a target region, e.g., an HIV infected cell; or (2) is preferentially passively absorbed by or entrained within a target tissue. The targeting group can be a small molecule, which is intended to include both non-peptides and peptides. The targeting group can also be a macromolecule, which includes, but is not limited to, saccharides, lectins, receptors, ligand for receptors, proteins such as BSA, antibodies, poly(ethers), dendrimers, poly(amino acids) and so forth.

Please replace the paragraph beginning on page 6, lines 1-5 with the following amended paragraph:

The term "cleavable group" is intended to mean a moiety that allows for release of a ~~quinolone~~pyrrolidone from a conjugate by cleaving a bond linking the ~~quinolone~~pyrrolidone (or ~~quinolone~~pyrrolidone linker arm construct) to the remainder of the conjugate. Such cleavage is either chemical in nature, or enzymatically mediated. Exemplary enzymatically cleavable groups include natural amino acids or peptide sequences that end with a natural amino acid.

Please replace the paragraph beginning on page 15, lines 14-15 and page 16, lines 1-6 with the following amended paragraph:

In another exemplary embodiment, at least one of $R^1$-$R^7$ is a linker moiety that includes a reactive functional group for conjugating the compound to another molecule or to a surface. The linkers of use in the compounds of the invention can also include a cleaveable group. In an exemplary embodiment, the cleaveable group is interposed between the ~~quinolone~~pyrrolidone core and a targeting agent or macromolecular backbone. Representative useful reactive groups are discussed in greater detail in succeeding sections. Additional information on useful reactive groups is known to those of skill in the art. *See*, for example, Hermanson, BIOCONJUGATE TECHNIQUES, Academic Press, San Diego, 1996.

Please replace the paragraph beginning on page 16, lines 8-17 with the following amended paragraph:

As discussed above, the ~~quinolone~~pyrrolidone core of the compounds of the invention are optionally tethered to other species by means of bonds formed between a reactive functional group on the ~~quinolone~~pyrrolidone or a linker attached to the ~~quinolone~~pyrrolidone, and a reactive functional group of complementary reactivity on the other species. For clarity of illustration the succeeding discussion focuses on the conjugation of representative ~~quinolone~~pyrrolidone of the invention to polymers, including poly(ethers) and dendrimers, and to targeting agents useful for translocating the ~~quinolone~~pyrrolidone -targeting agent conjugate across a membrane. The focus exemplifies selected embodiments of the invention from which others are readily inferred by one of skill in the art. No limitation of the invention is implied, by focusing the discussion on the representative embodiments.

Please replace the paragraph beginning on page 16, lines 18-22 with the following amended paragraph:

Exemplary ~~quinolones~~pyrrolidones of the invention bear a reactive functional group, which is generally located on the ~~quinolone~~pyrrolidone ring or on a substituted or unsubstituted alkyl or heteroalkyl chain attached to the ring, allowing their facile attachment to another species. A convenient location for the reactive group is the terminal position of an alkyl or heteroalkyl substituent of the ~~quinolone~~pyrrolidone core.

Please replace the paragraph beginning on page 21, lines 28-33 with the following amended paragraph:

In an exemplary embodiment, the invention provides a macromolecular, i.e., MW > 1000 D, conjugate between the ~~quinolone~~pyrrolidone core and a macromolecular species. In one embodiment, a macromolecular conjugate of the invention is formed by covalently conjugating a ~~quinolone~~pyrrolidone to a macromolecule via a reactive functional group. In another embodiment, the macromolecular conjugate is formed by a non-covalent interaction between a ~~quinolone~~pyrrolidone derivative and a macromolecule, e.g, a serum protein.

Please replace the paragraph beginning on page 22, lines 1-9 with the following amended paragraph:

In the following discussion, the invention is described by reference to specific macromolecules of use for forming conjugates with the novel ~~quinolone~~pyrrolidone cores of the invention. Those of skill in the art will appreciate that the focus of the discussion is for clarity of illustration and does not limit the scope of the invention. The invention provides macromolecular conjugates that include components derived from biomolecules and synthetic molecules. Exemplary biomolecules include polypeptides (e.g., antibodies, enzymes, receptors, antigens); polysaccharides (e.g., starches, inulin, dextran); lectins, non-peptide antigens and the like. Exemplary synthetic polymers include poly(acrylic acid), poly(lysine), poly(glutamic acid), poly(ethylene imine), etc.

Please replace the paragraph beginning on page 22, lines 12-17 with the following amended paragraph:

Selection of an appropriate reactive functional group on a ~~quinolone~~pyrrolidone core of the invention to form a desired macromolecular species is well within the abilities of one of skill in the art. Exemplary reactive functional groups of use in forming the covalent conjugates of the invention are discussed above. It is well within the abilities of one of skill to select and prepare a ~~quinolone~~pyrrolidone core of the invention having an appropriate reactive functional group of complementary reactivity to a reactive group on its conjugation partner.

Please replace the paragraph beginning on page 22, lines 18-27 with the following amended paragraph:

In one embodiment, the bond formed between reactive functional groups of the macromolecule and that of the ~~quinolone~~pyrrolidone attaches the ~~quinolone~~pyrrolidone to the macromolecule essentially irreversibly via a "stable bond" between the components. A "stable bond", as used herein, is a bond, which maintains its chemical integrity over a wide range of conditions (*e.g.*, amide, carbamate, carbon-carbon, ether, *etc.*). In another embodiment, a "cleaveable bond" links the macromolecule and the ~~quinolone~~pyrrolidone. A "cleaveable bond", as used herein, is a bond that undergoes scission under selected conditions. Cleaveable bonds include, but are not limited to, disulfide, imine, carbonate and ester bonds. As discussed in the preceding sections, the reactive functional group can be located at one or more positions of the ~~quinolone~~pyrrolidone.

Please replace the paragraph beginning on page 22, lines 30-34 to page 23, lines 1-6 with the following amended paragraph:

In an exemplary embodiment, the present invention provides conjugates between a ~~quinolone~~pyrrolidone core and saccharides, e.g., polysaccharides. In an exemplary embodiment, the invention provides a conjugate between a ~~quinolone~~pyrrolidone and inulin. Inulin is a naturally occurring polysaccharide, which has been previously investigated as a carrier for diagnostic moieties (Rongved, P. K., J. *Carbohydr. Res.* **1991**, *214*, 315; Corsi, D. M. V. E. et al., *Chem. Eur. J.* **2001**, *7*, 64). The structure of inulin can be described as a mixture of linear β-(2→1)-linked α-D-fructofuranosyl chains with a α-D-glucopyranosyl unit at the terminal end. Inulin is commercially available in a variety of molecular weights and the degree of

polymerization varies from 10 to 30, resulting in a molecular weight distribution of 1500 to 5000 Da. The high hydrophilicity, pH stability, low solution viscosity and biocompatability of inulin ensure that its conjugates have favorable pharmacological properties.

Please replace the paragraph beginning on page 23, lines 9-13 with the following amended paragraph:

In another aspect, the present invention provides a ~~quinolone~~pyrrolidone as set forth above, which is attached to a dendrimer via a reactive functional group. Similar to the polymeric group discussed above, the dendrimer has at least two reactive functional groups. In one embodiment, one or more formed ~~quinolone~~pyrrolidone is attached to the dendrimer. Alternatively, the ~~quinolone~~pyrrolidone is formed directly on the dendrimer.

Please replace the paragraph beginning on page 23, lines 14-19 with the following amended paragraph:

In an exemplary embodiment, a water-soluble and bio-adapted polyester (polypropionate) class of dendrimers has been designed to provide favorable pharmacokinetic properties. See, for example, Ihre, H. et al., *Macromolecules* **1998**, *31*, 4061; Ihre, H. et al., *J. Am. Chem. Soc.* **1996**, *118*, 6388; Anders, H., Ihre, H., Patent W0/9900440 (Sweden)). In an exemplary embodiment, the termini of the dendrimers are conjugated to a ~~quinolone~~pyrrolidone core of the invention.

Please replace the paragraph beginning on page 23, lines 22-35 with the following amended paragraph:

In another exemplary embodiment, the invention provides a conjugate between a ~~quinolone~~pyrrolidone core of the invention and poly(ethylene glycol). Poly(ethylene glycol) (PEG) is used in biotechnology and biomedical applications. The use of this agent has been reviewed (POLY(ETHYLENE GLYCOL) CHEMISTRY: BIOTECHNICAL AND BIOMEDICAL APPLICATIONS, J. M. Harris, Ed., Plenum Press, New York, 1992). Modification of enzymes (Chiu *et al.*, *J. Bioconjugate Chem.*, **4**: 290-295 (1993)), RGD peptides (Braatz *et al.*, *Bioconjugate Chem.*, **4**: 262-267 (1993)), liposomes (Zalipsky, *S. Bioconjugate Chem.*, **4**: 296-299 (1993)), and CD4-IgG glycoprotein (Chamow *et al.*, *Bioconjugate Chem.*, **4**: 133-140

(1993)) are some of the recent advances in the use of polyethylene glycol. Surfaces treated with PEG have been shown to resist protein deposition and have improved resistance to thrombogenicity when coated on blood contacting biomaterials (Merrill, "Poly(ethylene oxide) and Blood Contact: A Chronicle of One Laboratory," in POLY(ETHYLENE GLYCOL) CHEMISTRY: BIOTECHNICAL AND BIOMEDICAL APPLICATIONS, Harris, Ed., Plenum Press, New York, (1992), pp. 199-220).

Please replace the paragraph beginning on page 24, lines 1-6 with the following amended paragraph:

Many routes are available for attaching a ~~quinolone~~pyrrolidone core of the invention onto a polymeric or oligomeric species. *See*, for example, Dunn, R.L., *et al.*, Eds. POLYMERIC DRUGS AND DRUG DELIVERY SYSTEMS, ACS Symposium Series Vol. 469, American Chemical Society, Washington, D.C. 1991; Herren *et al., J. Colloid and Interfacial Science* **115**: 46-55 (1987); Nashabeh *et al., J. Chromatography* **559**: 367-383 (1991); Balachandar *et al., Langmuir* **6**: 1621-1627 (1990); and Burns *et al., Biomaterials* **19**: 423-440 (1998).

Please replace the paragraph beginning on page 24, lines 30-34 to page 25, lines 1-3 with the following amended paragraph:

The compounds of the invention are synthesized by an appropriate combination of generally well-known synthetic methods. Techniques useful in synthesizing the compounds of the invention are both readily apparent and accessible to those of skill in the relevant art. The discussion below is offered to illustrate certain of the diverse methods available for use in assembling the compounds of the invention, it is not intended to define the scope of reactions or reaction sequences that are useful in preparing the compounds of the present invention. Exemplary reaction schemes leading to the formation of ~~quinolones~~pyrrolidones of the invention are set forth below.

Please replace the paragraph beginning on page 37, lines 3-12 with the following amended paragraph:

As explained above, it has now been discovered that ~~quinolones~~pyrrolidones of the invention have anti-viral activity. As such, the compounds of the invention can be used to

inhibit a wide variety of viruses and, thus, to treat a wide variety of viral infections in a human. Viruses that can be inhibited using the compounds of the invention include, but are not limited, to DNA viruses, RNA viruses as well as retroviruses. Examples of viruses that can be inhibited using the compounds include, but are not limited to, Herpes viruses, Hepatitis (A, B and C) viruses, influenza viruses, POX viruses, Rhino viruses and HTLV (Human T-cell Leukemia) viruses (*e.g.*, HTLV 1 and 2). Based on their anti-viral activity, those of skill in the art are aware of other viruses that can be treated using compounds of the invention.